Received: 25 November 2019 | Revised: 22 December 2019 | Accepted: 3 January 2020

DOI: 10.1111/jce.14347

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Update on antiarrhythmic drug pharmacology

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Disclosures: None.

Funding information
Medical Research Council, UK, Grant/Award Numbers: G10002647, G1002082, MR/M001288/1; Wellcome Trust, UK, Grant/Award Number: 105727/Z/14/Z; British Heart Foundation, UK (BHF), Grant/Award Numbers: PG/11/59/29004, PG/12/21/29473, PG/14/79/31102, PG/14/80/31106, PG/15/12/31280, PG/16/67/32340, PG/19/59/34582; BHF Centres for Research Excellence [CRE] at Cambridge and Oxford; National Natural Science Foundation of China, Grant/Award Numbers: 31171085, 81770325, 81930105; Petplan Charitable Trust, UK; Engineering and Physical Sciences Research Council UK; Research England (KJ), UK

Abstract

Cardiac arrhythmias constitute a major public health problem. Pharmacological intervention remains mainstay to their clinical management. This, in turn, depends upon systematic drug classification schemes relating their molecular, cellular, and systems effects to clinical indications and therapeutic actions. This approach was first pioneered in the 1960s Vaughan-Williams classification. Subsequent progress in cardiac electrophysiological understanding led to a lag between the fundamental science and its clinical translation, partly addressed by The working group of the European Society of Cardiology (1991), which, however, did not emerge with formal classifications. We here utilize the recent Revised Oxford Classification Scheme to review antiarrhythmic drug pharmacology. We survey drugs and therapeutic targets offered by the more recently characterized ion channels, transporters, receptors, intracellular Ca^{2+} handling, and cell signaling molecules. These are organized into their strategic roles in cardiac electrophysiological function. Following analysis of the arrhythmic process itself, we consider (a) pharmacological agents directly targeting membrane function, particularly the Na^{+} and K^{+} ion channels underlying depolarizing and repolarizing events in the cardiac action potential. (b) We also consider agents that modify autonomic activity that, in turn, affects both the membrane and (c) the Ca^{2+} homeostatic and excitation-contraction coupling processes linking membrane excitation to contractile activation. Finally, we consider (d) drugs acting on more upstream energetic and structural remodeling processes currently the subject of clinical trials. Such systematic correlations of drug actions and arrhythmic mechanisms at different molecular to systems levels of cardiac function will facilitate current and future antiarrhythmic therapy.

KEYWORDS

antiarrhythmic drugs, cardiac arrhythmias, Modernized Oxford Classification, sicilian gambit, Vaughan-Williams

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1 | THE CLINICAL AND PRECLINICAL BACKGROUND: CLASSIFICATIONS OF ANTIARRHYTHMIC DRUGS

Cardiac arrhythmias constitute a major public health problem causing ~3.7 million deaths worldwide and significant clinical morbidity.[1] Pharmacological intervention remains the mainstay of their management despite major progress in interventional including ablation and device therapy. Much of this was informed by systematic drug development and classification, the latter relating modes of molecular, cellular, and systems actions to clinical indications and therapeutic effects. An early scheme classified then known antiarrhythmic drugs and their actions on different components of the cardiac action potential (AP).[2,3] Class I drugs reduced phase 0 slopes and overshoots, increasing, reducing, or conserving AP durations and effective refractory periods (ERP), respectively, through Na^+ channel block.[4] Class II drugs slowed sinoatrial node (SAN) pacing and atrioventricular node (AVN) AP conduction through β-adrenergic inhibition.[5,6] Class III drugs delayed phase 3 repolarization and effective refractoriness by K^+ channel block. Finally, class IV drugs reduced cardiac, particularly SAN and AVN, rate and conduction through L-type Ca^{2+} channel inhibition.[3]

The resulting simple yet coherent and pragmatic working model for cardiomyocyte function thus approached cardiac arrhythmia in terms of disrupted cardiac electrophysiological activation, correlating available therapies with then known arrhythmic targets (referenced in Lei et al[7]). It found widespread usefulness in diagnostic analysis and therapeutic action, directly facilitating clinical management and drug development.[8] Subsequent progress has expanded our electrophysiological understanding of both normal and arrhythmic cardiac excitation and its underlying membrane ion channel, intracellular ion transport, and receptor protein molecules,[9,10] and offered numerous novel pharmacological and therapeutic targets.[11] Yet, management of clinical arrhythmias has often lagged progress in other cardiological areas and may not have optimally benefitted from these fundamental scientific advances. The latter may reflect unmet needs for classification of these wide-ranging findings coherently relating fundamental physiological mechanisms to clinical applications. This was partly attempted by the European Society of Cardiology [12] which, however, did not emerge with a formal drug classification scheme.

2 | REVISED CLASSIFICATIONS OF PHARMACOLOGICAL ANTIARRHYTHMIC TARGETS: THE MODERNIZED OXFORD CLASSIFICATION

A recent modernized classification grouped currently available approved and investigational new drugs through their known molecular, ion channel, transporter, receptor, intracellular Ca^{2+} homeostatic, or cell signaling, targets (Figure 1A). It devised a format accomplishing a simultaneous classification of their actions on strategic aspects of cardiac electrophysiological function (Figure 1C). Of the latter processes, (a) the altered surface membrane excitability disrupting normal patterns of atrial or ventricular AP generation involving one or more component ion channel processes (Figure 2) constitutes the immediate source of arrhythmic phenomena. However, this interacts reciprocally with *cytosolic processes* involving (b) autonomic modulation, itself acting on both (a) and (c) excitation-contraction coupling. Drugs might also modify (d)

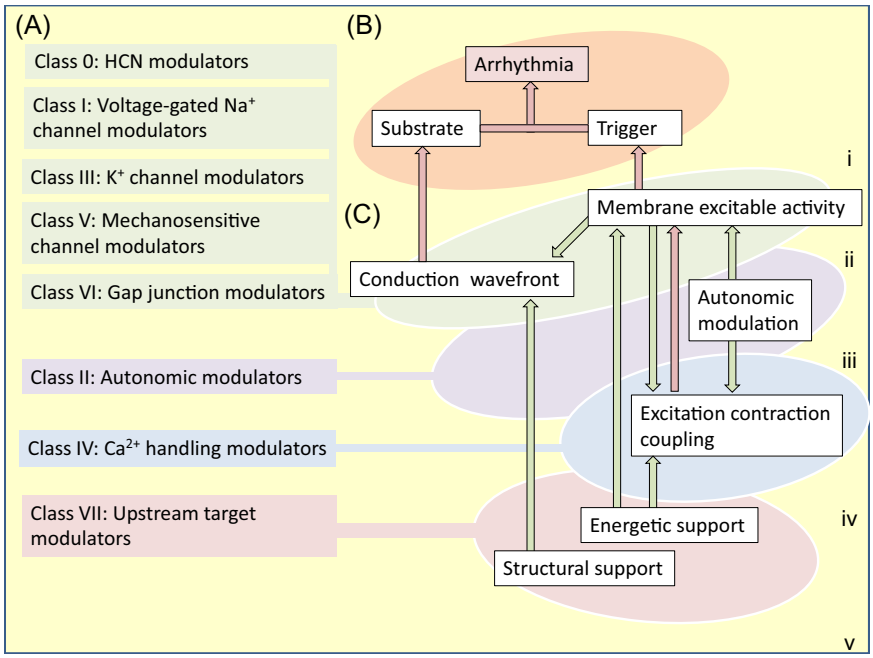

FIGURE 1 Modernized classification scheme[7,13] for currently available pharmacological agents directed at the treatment of arrhythmia, with a correlation of the relevant classes (A) acting on either arrhythmic trigger or substrate[14] (B), to the cascade of their underlying cellular membrane and physiological processes (Ci-iv).[11] HCN, hyperpolarization cyclic nucleotide

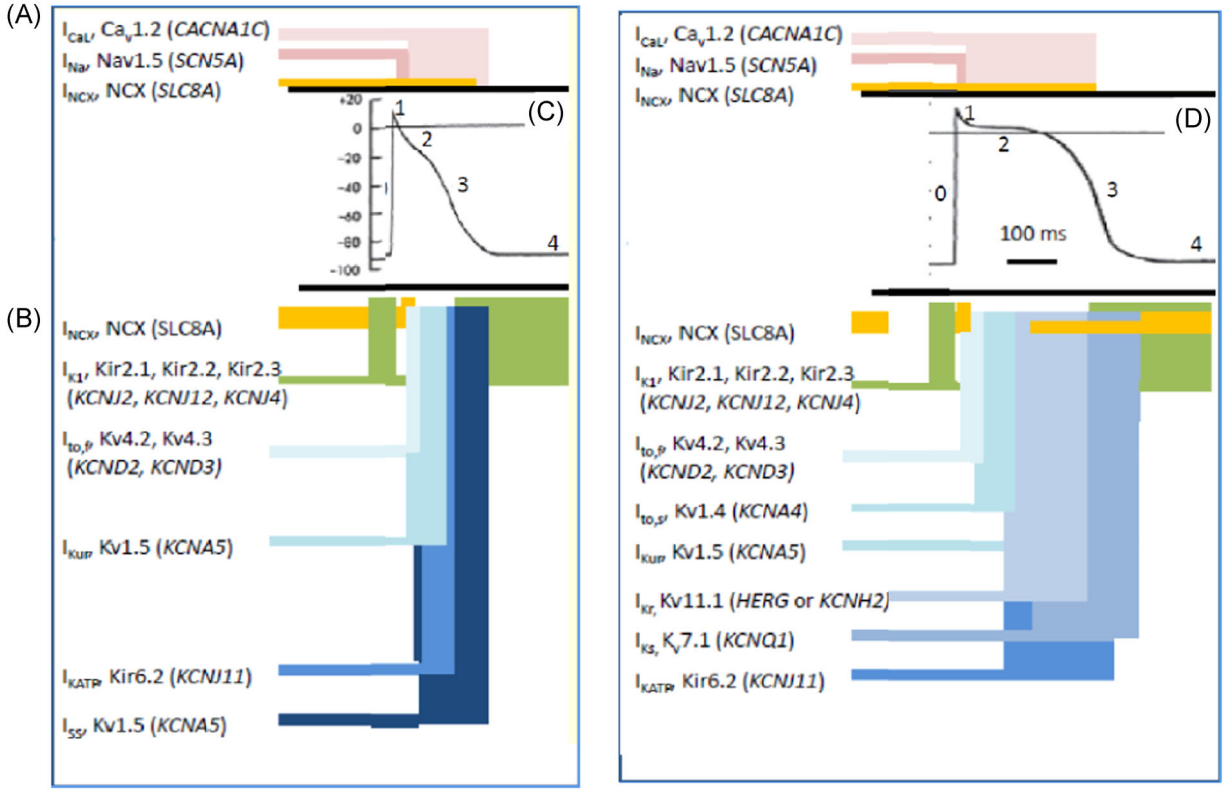

FIGURE 2 Membrane ion currents, listing their underlying proteins and encoding genes, underlying inward depolarizing (A) or outward repolarizing currents (B) producing the atrial (C) and ventricular (D) action potential, listing underlying membrane proteins and encoding genes[11]

more upstream energetic and remodeling structural processes often concerning cell signaling and intracellular metabolism, energetics and mitochondrial function, and fibrotic and inflammatory change (Figure 1C).

Finally, it nevertheless remained possible to pragmatically retain the original Vaughan-Williams classes I-IV,[7] expanding these classes and adding additional drug categories to complete its representation of the subsequent biomedical advance. Together with the more concise representation emphasizing clinically accepted as opposed to investigational new drugs (Table 1),[13] it, thus, represents a pragmatic modernization of the original Vaughan-Williams approach. It retained but added to Vaughan-Williams class I, recognizing recently reported late Na^+ current (I_{NaL}) components and their importance in long QT syndrome type 3. A broader class II captures advances in our understanding of autonomic, G-protein signaling, and an expanded class III, the many subsequently discovered K^+ channel subtypes. Class IV similarly encompasses recently demonstrated molecular targets and cellular physiological mechanisms related to Ca^{2+} homeostasis and excitation-contraction coupling. Further new classes recognize discoveries in cardiac automaticity (class 0), mechanically sensitive channels (class V), cell-cell electrotonic coupling (class VI), and physiological processes exerting longer term energetic changes and upstream structural remodeling (class VII). This classification thus categorized both clinically acceptable and potential sites of drug action relevant not only to current therapy but also future basic research and drug development.

3 | APPROVED DRUGS, DRUGS UNDER CLINICAL TRIAL, AND INVESTIGATIONAL NEW DRUGS IN THE MODERNIZED CLASSIFICATION

This scheme, thus, updated current views on clinically used and potential antiarrhythmic agents, facilitating the classification of drugs under trial, and future developments of investigational new drugs. This study primarily concerns drugs either impacting current practice or under trial for possible future practice, listed in a shortened version [13] of the scheme in the original report [7] in Table 1. Thus, Table 1 indicates that most drugs in classes 0, I, II, III, and IV of the classification scheme are accepted in one or more of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and National Institute for Clinical Excellence guidelines for management of patients with (a) ventricular arrhythmias and the prevention of sudden cardiac death,[18] (b) atrial fibrillation (AF),[17] and (c) supraventricular tachycardia.[19] Table 1 also summarizes their corresponding accepted therapeutic actions.[6,20–22]

Of the remainder, ranolazine (class Id), originally approved by the U.S. Food and Drug Administration for antianginal therapy, significantly reduced AF incidence in various clinical settings,[23–25] including paroxysmal AF (HARMONY trial [26]). There are trials on use,[29] and application in AF cardioversion [30] and comparisons against amiodarone[31,32] of the K1.5 channel-mediated ultrarapid K^+ current

TABLE 1 Current antiarrrhythmic drugs (after Lei et al[7,13])

Class	Drug exemplars	Pharmacological targets	Clinical indications	Therapeutic action
0		*HCN channel blockers*		
	Ivabradine	HCN channel mediated pacemaker current (I_f) inhibitor.	Stable angina and chronic cardiac failure with HR ≥ 70 beats/min. Potential new applications for tachyarrhythmias (*ACCF/AHA/NICE guidelines*[15]).	Reduced SAN automaticity.
I		*Voltage-gated Na^+ channel inhibitors*		
	Quinidine, ajmaline, disopyramide	Nav1.5 open state; intermediate (τ ~1-10 s) dissociation kinetics; often accompanying K^+ channel inhibition	Supraventricular tachyarrhythmias particularly recurrent AF. VT, VF (including SQTS and Brugada syndrome) (*ACCF/AHA/NICE guidelines*[16–19]).	Reduced ectopic ventricular/atrial automaticity and accessory pathway conduction. Increased refractory period, decreasing re-entrant tendency.[20–22]
	Lidocaine, mexiletine	Nav1.5 open state; rapid dissociation (τ ~0.1-1.0 s).I_{Na} window current	Ventricular tachyarrhythmias (VT, VF), particularly following myocardial infarction (*ACCF/AHA/NICE guidelines*[16,18]).	Reduced ectopic ventricular automaticity, DAD-induced triggered activity, and re-entrant tendency by converting unidirectional to bidirectional block, particularly in ischaemic partially depolarized myocardium.[20–22]
	Propafenone, flecainide	Nav1.5 inactivated state; slow dissociation (τ > 10 s).	Supraventricular tachyarrhythmias (AT, Af, AF, and tachycardias involving accessory pathways). Ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease, PVC, CPVT (*ACCF/AHA/NICE guidelines*[16–19]).	Reduced ectopic ventricular/atrial automaticity, DAD-induced triggered activity, and re-entrant tendency by converting unidirectional to bidirectional block. Slowed conduction and reduced excitability particularly at rapid heart rates blocking re-entrant pathways showing depressed conduction.[20–22]
	Ranolazine	Nav1.5 late I_{NaL} current.	Stable angina, VT. Potential new class of drugs for management of tachyarrhythmias, particularly in LQTS3 (*clinical trials related to antiarrhythmic effects*[23–26]).	Decreased AP recovery time and QT interval. Reduced EAD -induced triggered activity.
II		*Autonomic inhibitors and activators*		
	Nonselective, β-inhibitors: carvedilol, propranolol, nadolol; Selective β1-adrenergic receptor inhibitors: atenolol, bisoprolol, betaxolol, celiprolol, esmolol, metoprolol	Nonselective, β-, and selective β1-adrenergic receptor inhibitors	Sinus tachycardia or other types of tachycardic, including supraventricular (AF, Af, AT), arrhythmias. Rate control of AF, and ventricular tachyarrhythmias (VT, PVC). (Note. Atenolol, propranolol and nadolol also used in LQTS; nadolol used in CPVT) (*ACCF/AHA/NICE guidelines*[16–19]).	Reduced SAN, AVN and ectopic ventricular/atrial automaticity. Reduced EAD/DAD-induced triggered activity, SAN re-entry, and AVN conduction terminating re-entry.[6,21,22]
	Isoproterenol	Nonselective β adrenergic receptor activators	Congenital or acquired (often drug-related) Torsades de Pointes VT (*ACCF/AHA/NICE guidelines*[16–19]).	Suppressed EAD related triggered activity.[6,21,22]
	Atropine, anisodamine, hyoscine, scopolamine	Muscarinic M_2 receptor inhibitors	Mild or modulate symptomatic sinus bradycardia or AVN conduction inhibition (*ACCF/AHA/NICE guidelines*[16,19]).	Increased SAN automaticity and AVN conduction.[21,22]

	Carbachol, pilocarpine, methacholine, digoxin	Muscarinic M_2 receptor activators	Sinus tachycardia or supraventricular tachyarrhythmias (*ACCF/AHA/NICE guidelines*[16,19]).	Reduced SAN automaticity, SAN re-entry, and AVN conduction terminating re-entry.[21,22]
	Adenosine, ATP (Note: aminophylline acts as an adenosine receptor inhibitor).	Adenosine A_1 receptor activators	Sinus tachycardia, supraventricular tachyarrhythmias, frequent atrial or premature ventricular beats, cAMP-mediated triggered VT (*ACCF/AHA/NICE guidelines*[16,18,19]).	Reduced SAN automaticity, EAD/DAD-induced triggered activity, and AVN conduction, terminating re-entry.[21,22,27]
III		*K^+ channel inhibitors and openers*		
	Ambasilide, amiodarone, dronedarone	Nonselective K^+ channel inhibitors	VT in patients without structural heart disease, or with remote myocardial infarction, tachyarrhythmias with WPW. AF with AV conduction via accessory pathway; VF and PVC; tachyarrhythmias associated with supraventricular arrhythmias and AF (*ACCF/AHA/NICE guidelines*[16–19]).	Increased AP recovery time, and refractory period, decreasing re-entrant tendency.
				Note. Amiodarone also slows sinus node rate and AV conduction.[21,22]
	Dofetilide, ibutilide, sotalol	Kv11.1 (HERG) channel mediated rapid K^+ current (I_{Kr}) inhibitors	VT in patients without structural heart disease, or with remote myocardial infarction. Tachyarrhythmias associated with WPW syndrome. AF with AV conduction via accessory pathway, VF, PVC. Tachyarrhythmias associated with supraventricular arrhythmias and AF (*ACCF/AHA/NICE guidelines*[16–19]	Increased AP recovery time and refractory period, with decreased re-entrant tendency.[21,22,28]
	Vernakalant	Kv1.5 channel mediated, ultrarapid K^+ current (I_{Kur}) inhibitors	Acute conversion of AF (*clinical trials related to antiarrhythmic effects*[29–32]).	Increased atrial AP recovery time, and atrial refractory period, with decreased re-entrant tendency.[21]
	Nicorandil, pinacidil	Kir6.2 (I_{KATP}) openers	Nicorandil: Treatment of stable angina (second-line). (Note. Pinacidil: investigational drug for the treatment of hypertension).	Potentially decreased AP recovery time.
IV		*Ca^{2+} handling modulators*		
	Bepridil	Nonselective surface membrane Ca^{2+} channel inhibitors	Angina pectoris. Potential management of supraventricular tachyarrhythmias (*ACCF/AHA/NICE guidelines*[16,19]).	Reduced AVN conduction, terminating re-entry, and EAD/DAD-induced triggered activity.[6,21,22]
	Phenylalkylamines (eg, verapamil), Benzothiazepines (eg, diltiazem)	$Ca_v1.2$ and $Ca_v1.3$ channel mediated L-type Ca^{2+} current (I_{CaL}) inhibitors	Supraventricular arrhythmias and VT without structural heart disease. Rate control of AF (*ACCF/AHA/NICE guidelines*[16,18,19]).	Reduced AVN conduction, terminating re-entry, and EAD/DAD-induced triggered activity.[6,21,22]
	Flecainide	SR RyR2-Ca^{2+} channel inhibitors	Catecholaminergic polymorphic ventricular tachycardia (CPVT). (*clinical trials related to antiarrhythmic effects*[33–35])	Reduced DAD-induced triggered activity.[6,21,22]

(Continues)

TABLE 1 (Continued)

V		*Mechanosensitive channel inhibitors*		
	No clinically approved drugs in use			
VI		*Gap-junction channel inhibitors*		
	No clinically approved drugs in use			
VII		*Upstream target modulators*		
	Captopril, enalapril, delapril, ramipril, quinapril perindopril, lisinopril, benazepril, imidapril, trandolapril, cilazapril	Angiotensin-converting enzyme inhibitors	Management of hypertension, symptomatic heart failure. Potential application reducing arrhythmic substrate *(clinical trials related to antiarrhythmic effects*[36–38]).	Reduced structural and electrophysiological remodeling changes that compromise AP conduction and increase re-entrant tendency.
	Losartan, candesartan, eprosartan, telmisartan, irbesartan, olmesartan, valsartan, saprisartan	Angiotensin receptor inhibitors	Management of hypertension, symptomatic heart failure. Potential application reducing arrhythmic substrate *(clinical trials related to antiarrhythmic effects*[36,39,40]).	Reduced structural and electrophysiological remodeling changes that compromise AP conduction and increase re-entrant tendency.
	Eplerenone, spironolactone	Aldosterone receptor antagonists	Congestive cardiac failure *(clinical trials related to antiarrhythmic effects*[41–48]).	Potential reduction of arrhythmic substrate, including reduced fibrosis. K^+ sparing diuretic effect.
	Omega-3 fatty acids: eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid	Omega-3 fatty acids	Postmyocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms *(clinical trials related to antiarrhythmic effects*[49–51]).	Reduced structural and electrophysiological remodeling changes that compromise AP conduction and increase re-entrant tendency.
	Statins	3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors	Postmyocardial infarct reduction of risk of cardiac death, myocardial infarct, stroke, and abnormal cardiac rhythms *(clinical trials related to antiarrhythmic effects*[52–55]).	Reduced structural and electrophysiological remodeling changes that compromise AP conduction and increase re-entrant tendency.

Note: Of categories in the full classification,[7] classes V (mechanosensitive channel inhibitors), VI (gap junction channel inhibitors) and subclasses IIIc (transmitter-dependent K^+ channel inhibitors), IVc (sarcoplasmic reticular Ca^{2+}-ATPase activators), IVd (surface membrane ion exchange inhibitors), and IVe (phosphokinase and phosphorylase inhibitors) include investigational but not clinically approved drugs and are not listed here. In class III, nicorandil and pinacidil are approved drugs but not in use or clinical trials for antiarrhythmic therapy. Class VII (upstream target modulators) contains approved drugs not in current direct use for antiarrhythmic therapy, but for which clinical trials for antiarrhythmic actions are now available.

Abbreviations: ACCF, American College of Cardiology Foundation; AF, atrial fibrillation; Af, atrial flutter; AHA, American Heart Association; AP, action potential; AT, atrial tachycardia; AV, atrioventricular; AVN; atrioventricular node; cAMP, cyclic 3',5′-adenosine monophosphate; CPVT, catecholaminergic polymorphic ventricular tachycardia; DAD, delayed after depolarization; EAD, early after depolarization; HCN, hyperpolarization cyclic nucleotide activated channel; HR, heart rate; LQTS, long QT syndrome; NICE, National Institute for Clinical Excellence; PVC, premature ventricular contraction; SAN, sinoatrial node; SQTS, short-QT syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolf-Parkinson-White.

(I_{Kur}) blocker vernakalant. Flecainide, normally considered part of class Ic, was trialed in relationship to the management of catecholaminergic polymorphic ventricular tachycardia.[33–35] Although listed, clinical trials bearing on Kir6.2 (I_{KATP}) openers concern anginal rather than arrhythmia management. Table 1 is simplified in omitting the new classes V and VI as these only include investigational as opposed to clinically accepted drugs.

Finally, drugs in class VII are named in ACCF/AHA guidelines for the management of heart failure [15] but not in ACCF/AHA guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, AF, and supraventricular tachycardia. However, there exist clinical trials testing all its drug subcategories. Thus, a meta-analysis reported that both angiotensin-converting enzyme inhibitors and angiotensin receptor inhibitors (ARBs) produced ~28% reductions in AF risk in patients with left ventricular (LV) dysfunction or hypertrophy.[36] Clinical trials reported decreased AF in postmyocardial infarction patients with LV dysfunction with trandolapril,[37] and in patients with LV dysfunction with enalapril.[38] Ongoing clinical trials compared effects of telmisartan alone and in combination with ramipril (ONTARGET/TRANSCEND trial[39]), and clopidogrel with irbesartan in preventing vascular events (ACTIVE trial[40]). Of aldosterone receptor antagonists, a meta-analysis of seven reported trials of spironolactone and eplerenone demonstrated reduced episodes of ventricular premature complexes, and 21% and 72% reductions in sudden cardiac death and ventricular tachycardia.[41] Clinical trials reported positive antiarrhythmic effects of spironolactone in patients with[43,44] or without congestive heart failure [48] and of eplerenone in congestive heart failure due to idiopathic dilated or ischemic cardiomyopathy.[46]

More preliminary evidence implicates omega-3 fatty acids in reducing the incidence of AF (Mozaffarian et al[49] but see also Frost and Vestergaard[50]), particularly following coronary artery bypass surgery.[51] Finally, a meta-analysis suggested that 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors reduced AF incidence in three of three trials.[52] Statins reduced recurrent AF in 62 retrospectively studied lone persistent AF (≥3 months) patients after direct current cardioversion.[53] It lowered the rate of new AF development in prospectively studied coronary artery patients,[54] and AF development by 23% in patients prospectively enrolled in the multicenter Guidant-sponsored advancement heart failure registry.[55]

4 | ELECTROPHYSIOLOGICAL PROARRHYTHMIC MECHANISMS AS THERAPEUTIC TARGETS

Arrhythmias are the result of abnormal sinoatrial (SA), AVN, or Purkinje fiber automaticity, or pathological generation or conduction of excitation in atrial or ventricular cardiomyocytes. Sustained arrhythmia likely requires not only an initial trigger but also arrhythmic substrate typically arising from re-entry of excitation from active into recovered previously active myocardial regions (Figure 1B). It can take diverse forms in different cardiac regions each with distinct phenotypes. Successful therapeutic management of arrhythmias must, therefore, recognize this underlying mechanistic context bearing particularly upon cardiac AP generation, recovery, and/or its conduction.[56]

First, abnormal or altered AP generation can arise from altered *automaticity* underlying spontaneous, rhythmic SAN, or AVN or Purkinje tissue pacemaker activity. This could arise from altered slopes of the depolarization processes triggering successive APs or altered maximum diastolic or resting potentials. Changes in *normal automaticity* typically reflect alterations in pacemaker potentials driven by inward hyperpolarization cyclic nucleotide (HCN) mediated I_f and other ionic currents following normal adrenergic or cholinergic SAN pacemaker stimulation or inhibition. *Abnormal automaticity* arises from spontaneous impulses generated in partially depolarized fibers in pathological circumstances; this can even involve normally nonautomatic atrial and ventricular muscle. This causes an automatic, often tachycardic, firing distinct from the SAN activity, exemplified by ectopic atrial tachycardias, accelerated idioventricular rhythms and ventricular tachycardias.

Second, the *triggered activity* can be initiated by membrane potential after depolarization events whose amplitude is sufficient to initiate regenerative Na^+ or Ca^{2+} channel excitation. *Early after-depolarization* (EAD) events typically occur under bradycardic conditions, when altered balances of inward Na^+ or Ca^{2+} and outward K^+ current prolong the AP. This permits Ca^{2+} current reactivation, in turn, triggering an extrasystolic AP potentially leading to torsades de pointes. *Delayed after-depolarization* (DAD) events following full AP repolarization result from transient inward currents, I_{ti}, resulting from enhanced electrogenic Na^+/Ca^{2+} exchange activity when this is increased by elevations in cytosolic Ca^{2+} concentrations due to abnormal diastolic sarcoplasmic reticular (SR) Ca^{2+} release.[11,14]

Third, abnormal AP *conduction slowing* can follow functional reductions in inward Na^+ current initiating the AP and driving its propagation. It can also result from anatomical changes altering tissue electrical resistance compromising the local circuit currents taking place through connexin channels, and propagating the AP. Either can involve either functionally or anatomically defined pathways.[57] Actual conduction block can be associated with heterogeneities in refractoriness and conduction in particular parts of such a circuit. These heterogeneities could be varying with time and previous impulse activation, or over anatomically or functionally consistent or defined paths. These often result in regions of unidirectional conduction block.

Altered AP conduction is then often associated with a presence of *re-entrant substrate* perpetuating previously triggered arrhythmias.[58] Re-entry can also occur with abnormal AP recovery reflecting altered relationships between the time intervals between AP recovery, refractoriness, and repolarization reserve. It has, thus, been associated with the presence of discrepancies between ERPs and AP recovery times as exemplified in LQT syndromes.[14] Either spatial heterogeneities, exemplified by transmural gradients, or temporal heterogeneities, most frequently manifest as alternans in

these parameters, and would accentuate other proarrhythmic effects.[11,59–61]

Proarrhythmic effects of isolated, decay, or block of *impulse conduction* can also occur in the absence of re-entrant pathways. This is exemplified by the SA conduction block permitting escape of a supraventricular or ventricular focus then generating abnormal impulses. Similar phenomena could follow delayed or completely blocked AV conduction.

5 | THERAPEUTIC TARGETS: ION CURRENT EXCITATION AND THE AP PROPAGATION WAVEFRONT

The functional unit of excitable activity in the cardiomyocyte is the propagating AP (Figure 2). Typical AP waveforms comprise rapid depolarizing (phase 0), early repolarising (phase 1), brief atrial and prolonged ventricular plateaus (phase 2), late repolarizations (phase 3), and end in electrical diastole (phase 4). Phase 0 AP initiation beginning this sequence of events requires inward Na^+ current activation (Figure 2A); Ca^{2+} channel activation contributes to the phase 2 plateau contribution, and is more prominent in ventricular than atrial muscle and is considered in the next section. AP generation through the heart is initiated from *pacemaker activity* in the SAN which possesses an I_f current, for which a new drug class 0 affecting such periodic generation of electrical activity and therefore heart rate has been introduced. Heart rate reduction also offers a therapeutic strategy for managing acute cardiac ischemia.

Of drugs directed at the *inward Na^+ current* responsible for the *depolarization* phase 0 of the AP, class Ia drugs preferentially bind to the open state of the Nav1.5 Na^+ channel with a dissociation time constant of τ ~1 to 10 seconds. They, thus, inhibit AV conduction and increase the ERP. They also exhibit a concomitant K^+ channel block which increases AP duration. Together these properties reduce re-entrant tendency. Class Ib agents contrastingly bind preferentially to the inactivated state of the Na^+ channel from which they more rapidly dissociate over τ ~0.1 to 1.0 seconds. The latter minimizes the duration of their actions within and through successive cardiac cycles. This explains their effectiveness in preventing arrhythmias in ventricular tissue, whose Na^+ channels remain inactive for the longest duration amongst cardiomyocyte types reflecting the duration of the AP plateau. There they block Nav1.5 window current, shortening AP duration and increasing ERP. They are useful in cardiac ischaemic situations where there is Na^+ channel inactivation. Class Ic drugs bind to inactivated channels but dissociate slowly, over τ greater than 10 seconds. This results in a use-dependent channel block, particularly under conditions of high-channel activation frequencies. They, thus, produce a generalized reduction in cardiac excitability with widespread effects, including slowing AV conduction, but do so while exerting a little effect on AP duration. Atrial Na^+ channels remain open for longer than in the ventricles, and so class Ia and Ic drugs have been used to prevent supraventricular arrhythmias.[62]

Finally, the new class Id recognizes recently developed agents acting on the late Na^+ current (I_{NaL}). These drugs are of potential importance for managing proarrhythmic situations under conditions of reduced repolarization reserve as in long QT syndrome 3, and pathological bradycardic and ischaemic conditions, and cardiac failure. They shorten AP recovery and increase refractoriness and repolarization reserve.[63]

AP *repolarization* ultimately restoring the background resting potential is driven by a range of *outward K^+ currents* (Figure 2B).[11,64] An expanded class III reflects the considerable progress in our understanding of K^+ channel subtypes.[64–68] Thus, phase 0 depolarization is rapidly terminated by transient outward Kv4.3 and Kv4.2-mediated I_{to} currents driving the early-phase 1 AP repolarization. In atrial myocytes (Figure 2C), the prominent I_{to} and the atrial-specific Kv1.5 (*KCNA5)* mediated ultrarapid I_{Kur}, as well as the GIRK1 and GIRK4 mediated acetylcholine-sensitive I_{KACh} together ensure the relatively shorter atrial APs. In ventricular myocytes (Figure 2D), the Kv11.1 (HERG or *KCNH2)* mediated I_{Kr} rapidly activates with phase 0 AP depolarization, then rapidly inactivates over AP phases 0 to 2.[69,70] Phase 3 repolarization then reopens the channel driving outward phase 3 and early-phase 4 currents that terminate the plateau. The more slowly activating Kv7.1 (*KCNQ1*) mediated I_{Ks} increases over phase 2 to become a major relatively persistent phase 3 K^+ conductance. Kir2.1, Kir2.2, and Kir2.3 (*KCNJ2*, *KCNJ12* and *KCNJ4)* mediated inward rectifying I_{K1} reduces K^+ conductance at voltages positive to −20 mV in phases 0 to 2. In contrast, it produces outward currents with repolarization to voltages more negative than −40 mV late in phase 3, and stabilizes phase 4 diastolic resting potentials. The latter are also stabilized by background $K_{2P}2.1$ (*KCNK2*, expressing K_{2P} currents), and the normally small ATP-sensitive Kir6.2 (*KCNJ11)* mediating I_{KATP}. However, the latter can be activated by reduced intracellular ATP levels.[71] Finally, the ERP extends beyond each AP. This can increase with Na^+ channel inhibition delaying the point at which a critical proportion of Na^+ channels has recovered, or with AP prolongation.

The new class V of *mechanosensitive channel blockers* are selective for cation-selective and a number of mechanosensitive ion channel types that include TRPC3 or TRPC6. However, they do not include currently clinically utilized drugs; their available exemplars are confined to investigational new drugs. The latter is also true for class VI *gap junction modulators*, despite the importance of gap junction intercellular conductance between cardiomyocytes in cell-to-cell coupling. The latter is key to ventricular conduction, of central importance in the generation of the re-entrant substrate. Thus, its underlying proarrhythmic AP conduction slowing can result follow not only from compromised AP activation due to reduced inward Na^+ current but also anatomical changes altering connexin (Cx)-dependent intercellular conductances.[8]

AP depolarization produces a coherent wave of excitation followed by refractoriness often propagating through often anisotropic gap junction connexin connections between successive SAN, atrial, AV, Purkinje, and endocardial and epicardial ventricular cardiomyocytes, respectively, with detailed AP waveforms varying

with cell type. Thus, atrial cells show shorter APs than ventricular cells, reflecting their large repolarizing, transient outward voltage-dependent, and acetylcholine-sensitive K^+ currents (Figure 2C,D).[57,61,72]

6 | THERAPEUTIC TARGETS: Ca^{2+} HOMEOSTASIS AND EXCITATION-CONTRACTION COUPLING

Figure 3 summarizes recent reports suggesting reciprocal mechanistic relationships between the membrane excitation described above, and particular component excitation-contraction coupling processes whose activation connects surface electrical activation to the initiation of mechanical activity. It, thus, represents the substantial progress made in the understanding of this area following Vaughan-Williams's original studies. Thus, membrane excitation includes a depolarization-induced phase 2 activation of transverse tubular L-type Ca^{2+} current I_{CaL} in turn responsible for the AP plateau phase. These Ca^{2+} currents also *feed-forward* to initiation of cardiac excitation-contraction coupling. The resulting local elevations in cytosolic Ca^{2+}concentration trigger a Ca^{2+}-induced ryanodine receptor (RyR2)-mediated SR Ca^{2+} release, thereby synchronized to the membrane excitation events (Figure 3C).[73,74] The resulting elevated cytosolic Ca^{2+} concentrations result in the troponin mediated activation of mechanical activity. Termination of this Ca^{2+} release process normally takes place with membrane repolarization. The cytosolic Ca^{2+} concentration is then returned to its resting level by both SR membrane Ca^{2+}-ATPase mediated Ca^{2+} re-uptake returning Ca^{2+} into the SR and the surface membrane Na^+-Ca^{2+} exchanger which expels Ca^{2+} from the cytosol into the extracellular space in return for extracellular Na^+ entry.[75] Thus, the cycles of increase followed by restoration of cytosolic Ca^{2+} concentration are normally synchronized with membrane events associated with the AP. The overall energetic cost is defrayed by the metabolically dependent mitochondrial generation of cellular ATP.[76]

However, the processes involved in intracellular Ca^{2+} homeostasis can show proarrhythmic events independent of such surface membrane control. They can also actually exert potentially proarrhythmic *feedback* effects on their initiating membrane events. First, altered Ca^{2+} channel function itself may predispose to initiation of proarrhythmic EAD phenomena late in phase 2 or early in phase 3 of the AP particularly in the presence of AP prolongation as might occur in long QT syndromes. These would, in turn, result in extrasystolic membrane excitation. Second, elevated sarcoplasmic Ca^{2+} concentrations resulting from increased Ca^{2+} channel or mechanosensitive channel activity, or RyR2-Ca^{2+} sensitivity, can themselves trigger propagating waves of spontaneous SR Ca^{2+} release asynchronous to

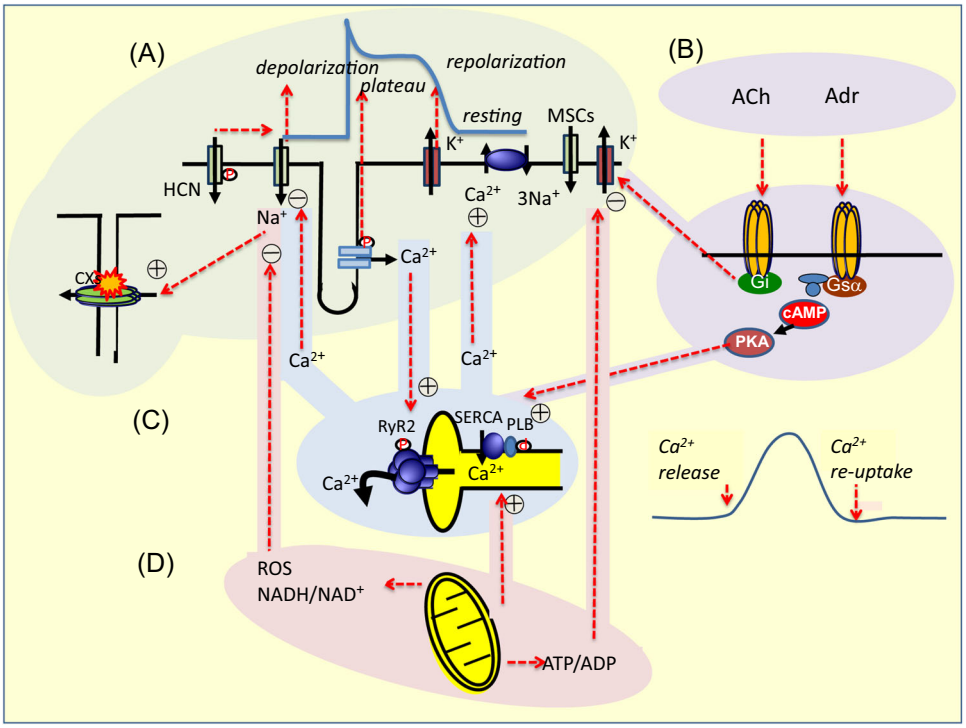

FIGURE 3 Surface and intracellular membrane ion channels, ion exchangers, transporters, autonomic receptors, and ionic pumps involved in cardiomyocyte physiological excitation and activation forming established or potential pharmacological targets underlying membrane (A) and autonomic signaling (B), excitation-contraction coupling (C) and upstream energetic or structural remodeling targets (D). ACh, acetylcholine; Adr, adrenaline; cAMP, cyclic 3′5-adenosine monophosphate; Cx: connexin; G_i: inhibitory G-protein; G_s stimulatory G-protein; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; MSC, mechanically sensitive channel; Na^+, K^+, Ca^{2+}, and Ca^{2+}/$3Na^+$ fluxes through Nav1.5/Na^+, Kv/K^+, Cav/Ca^{2+} channel, and Na^+/Ca^{2+} exchanger proteins; PKA, protein kinase A; ROS, reactive oxygen species; RyR2: cardiac ryanodine receptor, type 2; SERCA: sarcoplasmic reticular Ca^{2+} ATPase

the normal cycles of membrane excitation. These can lead to elevated cytosolic Ca^{2+} concentrations. The latter can result in increased electrogenic Na^+/Ca^{2+} exchange activity. This drives a depolarizing transient inward current I_{TI}. The latter may result in proarrhythmic DADs following full AP repolarization.[75] Third, elevations in cytosolic Ca^{2+} concentration have been associated with downregulated longer term Na^+ channel expression and function compromising AP conduction velocity.[77] Finally, the depolarizing electrogenic effects of Na^+/Ca^{2+} exchange may contribute to SAN automaticity.[78]

These recent advances have, thus, considerably broadened the range of potential therapeutic targets concerned with such Ca^{2+} homeostasis and its modulation. They hold future promise of agents directed at (a) surface membrane L- and/or T-type Ca^{2+} channels, (b) intracellular RyR and inositol trisphosphate receptor-Ca^{2+} channels, (c) SR Ca^{2+}-ATPase activity, (d) ion exchange, particularly Na^+-Ca^{2+} exchange processes, and (e) phosphorylation levels of cytosolic Ca^{2+} handling proteins, including CamKII inhibitors and P21 activated kinase 1 (PAK1) modulators. However, in this group, only Ca^{2+} channel blockers and one RyR2-blocker, flecainide, which has found recent use in monotherapy of catecholaminergic polymorphic ventricular tachycardia (CPVT) are currently clinically available.

7 | THERAPEUTIC TARGETS: AUTONOMIC MODULATORS

Figure 3B illustrates the various relationships between autonomic inputs and the processes outlined below in retention and broadening of Vaughan-Williams class II beyond its originally listed sympathetic β-adrenergic effects. This reflects progress in the understanding of the wide range of modulators acting upon the widely expressed cell surface membrane guanine nucleotide-binding protein (G-protein)-coupled receptors (GPCRs). The latter have been successfully exploited in a variety of other therapeutic applications. Thus, in addition to the selective and nonselective adrenergic antagonists are adenosine receptor and cholinergic muscarinic receptor modulators,[6] and a possibility of future potential targets amongst the ~150 remaining orphan GPCRs. The updated G-protein mechanisms have wide actions on both the excitation-contraction coupling and the surface membrane groups of functions.

First, β-adrenergic receptor activation produces multiple, inotropic, chronotropic, and lusitropic effects upon cardiac function[73] through G_s-protein and adenylate cyclase activation increasing cytosolic cyclic 3′5′-adenosine monophosphate concentrations $(cAMP)_i$. The latter promotes protein kinase A (PKA) mediated phosphorylation actions on a wide range of ion channels including the Nav1.5 Na^+ channel, Kv11.1 and Kv7.1 K^+ channel species mediating rapid and slow, I_{Kr} and I_{Ks}, K^+ currents, and Cav1.2 and Cav1.3 L-type Ca^{2+} channels mediating I_{CaL} and the RyR2 SR Ca^{2+} release channel. cAMP also directly enhances the HCN channel and consequently pacemaker I_f current activity. Finally, exchange proteins directly activated by cAMP also likely trigger a proarrhythmic RyR2-mediated Ca^{2+} release.[79]

Second, of further G-protein subtypes, Table 1 now incorporates drugs targeted at G_i protein-mediated parasympathetic cholinergic muscarinic (M_2) or adenosine (A_1) receptor activation, conversely reducing membrane excitation. These actions occur in the SAN, AVN, or atrial myocardium even in the absence, but in ventricular tissue only in the presence, of pre-existing adrenergic challenge. The G_i activation causes a G protein βγ subunit mediated opening of inward rectifying I_{KACh} or I_{KAdo} channels particularly in supraventricular tissue, through actions on their GIRK1 and GIRK4 components.[65,80,81] G_i activation also inhibits adenylyl cyclase reducing $(cAMP)_i$ and its associated increases in I_{CaL} and I_f. It may also upregulate protein phosphatase 2-mediated dephosphorylation at PKA phosphorylation sites.[82,83]

These updates prompt class II subclassifications of the clinically used nonselective and selective β1-adrenergic receptor inhibitors carvedilol, propranolol and nadolol, and atenolol and bisoprolol, respectively. To this are added the nonselective β-adrenergic receptor activators isoproterenol, reflecting the G_s-protein and adenylate cyclase modulation, and new subclasses also representing drugs acting through G_i protein.

8 | POSSIBLE THERAPEUTIC TARGETS: UPSTREAM MODULATORS OF ENERGETIC STATUS AND STRUCTURAL REMODELING

Processes affecting long-term cellular energetics and remodeling of tissue structure (Figures 1D and 3D) contrast with the primary preoccupation with the *acute* effects on specific ion channels in the original Vaughan-Williams classification. Thus, rather than direct effects on arrhythmic processes, the drugs included in class VII are normally indicated for cardiovascular conditions, such as hypertension, coronary artery disease, and heart failure that do not primarily result in arrhythmias. Nevertheless, such specific conditions and the general categories of changes related to oxidative stress as well as longer term structural fibrotic, hypertrophic, inflammatory, changes upstream of the electrophysiological processes at the membrane level have been associated with AF.[84–86]

Metabolic stress associated with cardiovascular conditions, such as hypertrophic change, cardiac failure, and ischaemia-reperfusion,[87–90] and biochemical conditions including obesity, insulin resistance, and type 2 diabetes are, thus, accompanied by energetic, particularly mitochondrial, dysfunction.[91–93] The consequent destabilization of inner membrane potentials required to drive the electron transport chain compromises ATP synthesis. ATP depletion or increased ADP increases sarcolemmal ATP-sensitive K^+ channel ($sarcK_{ATP}$) open probabilities.[94] This shortens AP duration, potentially producing proarrhythmic re-entrant substrate,[95,96] and hyperpolarizes cell membrane potentials compromising cell excitability and AP propagation.[94]

Compromised mitochondrial function also increases reactive oxygen species (ROS)-induced ROS release; ROS exert a wide range of potentially arrhythmogenic channel actions bearing upon cell-cell coupling,[97] AP conduction,[98] repolarization,[99] alternans,[100] and Ca^{2+}

-mediated triggers.[90] They decrease I_{Na}[98] and I_K,[99] activate sarcolemmal K_{ATP} channels,[101] modify Na^+ and L-type Ca^{2+} channel inactivation, increase I_{NaL}, and oxidize RyR2. The latter results in an increased SR Ca^{2+} leak, altering intracellular Ca^{2+} cycling.[76,90,102] They also reduce Cx43 trafficking and function.[94,103,104]

Atrial fibrosis is a potential source of arrhythmic substrate leading to AF; fibrotic change also accompanies some Na^+ channelopathies.[105,106] A significant proportion of pharmacological agents that might influence this is known to act on the renin-angiotensin system. In the present context, rather than its immediate cardiovascular pressor effects, they likely relate to its effects on cardiac remodeling. Thus, angiotensin II, through AT1 may trigger fibroblast proliferation associated with increased transforming growth factor-β release. This promotes fibrotic and/or hypertrophic change which AT1 receptor antagonists are reported to reduce. Angiotensin II has also been reported to affect cardiac electrical activity including gap-junction mediated impulse propagation. Finally, AT1 receptor activation has been reported to upregulate ROS with inflammatory as well as mitochondrial effects. Preliminary evidence suggests that the currently available drugs listed including angiotensin-converting enzyme and AT blockers, aldosterone receptor antagonists, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), and n-3 (ω-3) polyunsaturated fatty acids may reduce such structural and electrophysiological remodeling.[85]

Further future upstream targets are likely to emerge. For example, the key cardiomyocyte regulator of ion channel activity, Ca^{2+} homeostasis and cardiac contractility,[82,83,107] PAK1, has been reported to cardio-protect through signaling processes inhibiting maladaptive, proarrhythmic, hypertrophic remodeling, and progression in cardiac failure.[108] This offers potential novel clinical therapeutic strategies.[109,110]

9 | RECAPITULATION

Cardiac arrhythmias constitute a major clinical problem, and pharmacological intervention remains the mainstay of their clinical management. Rational drug use relies on a fundamental understanding of drug modes of action through the cellular, systems, and clinical levels and clear correlations of these with their clinical indications and therapeutic actions. This, thus, further involves their systematic classification relating these scientific and clinical issues within a rational framework. This study surveys current clinically established antiarrhythmic drugs in light of pharmacological developments that followed the historic Vaughan-Williams classification of such agents. It utilizes the major progress in our understanding of cardiac electrophysiology, its contained mechanisms, and its molecular and physiological basis in a large number of underlying membrane ion channels, intracellular ion transport, and autonomic receptor, and effector protein molecules underlying normal and abnormal cardiac function. It places these within a recently introduced classification scheme systematizing their pharmacological targets in light of recent biomedical advances. The latter, in turn, are grouped into categories of electrophysiological effects and their direct or indirect convergence upon their primary arrhythmic mechanisms. Such a systematic approach may facilitate current and future antiarrhythmic therapy.

ACKNOWLEDGMENTS

This study was supported by Medical Research Council, UK (MR/M001288/1, CLHH; G10002647, G1002082, ML), Wellcome Trust, UK (105727/Z/14/Z, CLHH), British Heart Foundation, UK (BHF) (PG/19/59/34582, PG/14/79/31102, PG/15/12/31280, PG/14/80/31106, PG/16/67/32340, PG/12/21/29473, and PG/11/59/29004, and BHF Centres for Research Excellence [CRE] at Cambridge and Oxford, CLHH, and BHF CRE at Oxford, ML), National Natural Science Foundation of China (31171085, ML; 81930105 and 81770325, LW), Petplan Charitable Trust, UK (KJ, CLHH), Engineering and Physical Sciences Research Council UK, and Research England (KJ), UK.

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How to cite this article: Huang CL-H, Wu L, Jeevaratnam K, Lei M. Update on antiarrhythmic drug pharmacology. *J Cardiovasc Electrophysiol*. 2020;31:579–592. https://doi.org/10.1111/jce.14347